INTELLECTUAL PROPERTY LAW OFFICES
WEINER & BURT, P.C.

635 N. US 23
P.O. BOX 186
HARRISVILLE, MICHIGAN 48740

Tel. (517) 724-7400 or (800) 872-8368
Fax (517) 724-7100
E-mail: wab@voyager.net

IRVING M. WEINER*
PAMELA S. BURT*
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August 17, 2000

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D. C. 20231

Sir:

Please file the enclosed application for Letters Patent identified as:

Inventors: JOHN D. KUTZKO, MICHAEAL G. SINGER & JOHN McMICHAEL
Title: "Method and System for Use In Treating A Patient with an Anticoagulant to Optimize Therapy and Prevent an Adverse Drug Response" and including: Specification, Claims and Abstract; Declaration & Power of Attorney; Verified Statements re Small Entity Status (Inventors/Small Business Concern)
Drawings: 2 sheets Formal
PTO-2038 for filing fee;
PTO-1619 A;
Assignment;
PTO-2038 for assignment recorded.

Respectfully submitted,

Irving M. Weiner, Reg. No.22168

IMW/kk
Enclosures

CERTIFICATE OF MAILING

I hereby certify that this New Application Transmittal and the documents referred to as attached therein are being deposited with the Postal Service on August 17, 2000, by mail addressed to Box PATENT APPLICATION, Assistant Commissioner for Patents, Washington D.C. 20231.

PTO/SB/09 (12-97)
Approved for use through 9/30/00. OMB 0651-0031
Patent and Trademark Office, US DEPARTMENT OF COMMERC

STATEMENT CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(F) & 127(B))--INDEPENDENT INVENTOR

Docket Number (Optional)
SMG200A1

Applicant, Patentee, or Identifier: John D. Kutzko, Michaeal G Singer, and John McMichael

Application or Patent No:

Filed or Issued:

Title: Method and System for Use in Treating a Patient with an Anticoagulant to Optimize Therapy and Prevent an Adverse Drug Response

As a below named inventor, I hereby state that I quality as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees to the Patent and Trademark Office described in:

- [X] the specification filed herewith with title as listed above
- [ ] the application identified above
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I have not assigned, granted, conveyed, or licensed, and am under no obligation under contract or law to assign, grant, convey, or license, any rights in the invention to any person who would not quality as an independent inventor under 37 CFR 1.9(d) or a non profit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed or licensed or am under an obligation under contract or law to assign, grant, convey or license any rights in the invention is listed below:

- [ ] No such person, concern or organization exists.
- [X] Each such person, concern, or organization is listed below.

The RxFiles.Net Corporation

Separate statements are required from each named person, concern, or organization having rights to the invention stating their status as small entities. (37 CFR 1.27).

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

John D. Kutzko	Michaeal G. Singer	John McMichael
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
Signature of Inventor	Signature of Inventor	Signature of Inventor
8/8/00	8/8/00	8/8/00
Date	Date	Date

PTO/SB/09 (12-97)
Approved for use through 9/3/00 OMB 0651-0031
Patent and Trademark Office; US DEPARTMENT OF COMMERC

STATEMENT CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) & 127(c))– SMALL BUSINESS CONCERN

Docket Number (Optional)
SMG200A1

Applicant, Patentee, or Identifier: John D. Kutzko, Michaeal G Singer, and John McMichael
Application or Patent No:_____
Filed or Issued:_____
Title: Method and System for Use in Treating a Patient with an Anticoagulant to Optimize Therapy and Prevent an Adverse Drug Response

I hereby state that I am

☐ the owner of the small business concern identified below:

☒ an official of the small business concern empowered to act on behalf of the concern identified below

NAME OF SMALL BUSINESS CONCERN: The RxFiles.Net Corporation

ADDRESS OF SMALL BUSINESS CONCERN: 342 South Tamiami Trail
Nokomis, Florida 34275

I hereby state that the above identified small business concern qualifies as a small business concern as defined in 13 CFR Part 121 for purposes of paying reduced fees to the United States Patent and Trademark Office. Questions related to size standards for a small business concern may be directed to: Small Business Administration, Size Standards Staff, 409 Third Street, SW, Washington DC 20416.

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☐ the application identified above.

☐ the patent identified above.

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Each person, concern, or organization having any rights in the invention is listed below:

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☐ NONE

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NAME OF PERSON SIGNING: Michaeal G. Singer

TITLE OF PERSON IF OTHER THAN OWNER: President

ADDRESS OF PERSON SIGNING: 705 S. Lake Huron Shore Rd., Harrisville, MI 48740

SIGNATURE_____ DATE 8/8/00

METHOD AND SYSTEM FOR USE IN TREATING A PATIENT WITH AN ANTICOAGULANT TO OPTIMIZE THERAPY AND PREVENT AN ADVERSE DRUG RESPONSE

RELATED APPLICATION

The present patent application is a continuation-in-part of United States Patent Application Serial Number 09/348,592 filed on July 6, 1999, the entire contents of which are incorporated herein by reference thereto.

FIELD OF THE INVENTION

The present invention relates generally to a method and system for use in treating a patient with an anticoagulant to optimize drug therapy and to prevent an adverse drug response. More particularly, the present invention relates to a method and system for use in treating a patient with Coumadin® or a substance containing warfarin. The present invention can utilize either drug levels or other surrogate markers to determine the effectiveness of the dosing regimen and, if necessary, to suggest a new more optimal drug dose.

The term "anticoagulant" as used herein includes, but is not limited to, warfarin, Coumadin®, heparin, warfarin sodium salt, coumarin derivatives, indandione derivatives, dicumarol, anisindione, phenindione, ethyl bicoumacetate, bishydroxycoumarin, abcimixab, Reopro®, actilyse, alteplase, Activase®, anagrelide, Agrylin®, anistreplase, Eminase®, antithrombin III, Thrombate III®, ardeparin, Normiflo®, argatroban, clopidrogel, Plavix®, dalteparin, Fragmin®,

danaparoid, Orgaran®, dipyridamole, Persantine®, dipyridamole/aspirin, Aggrenox®, duteplase, enoxaparin, Lovenox®, eptifibatide, Integrilin®, lepirudin, Refludan®, nadroparin, Fraxiparine®, oprelvekin, Neumega®, pentosan polysulfate sodium, Elmiron®, reteplase, Retavase®, reviparin, Clivarine®, saruplase, streptokinase, Kabikinase®, Streptase®, tinzaparin, Innohep®, tirofiban, Aggrastat®, unfractionated heparin, low molecular weight heparin, all antithrombotic agents, all vitamin K antagonists, and all substances derived from and/or related to the foregoing substances.

Furthermore, wherever the generic term "anticoagulant" is used herein it is also intended to mean species which employ any or more of the individual anticoagulants as defined and/or alluded to hereinabove.

BACKGROUND OF THE INVENTION

When a patient begins taking an anticoagulant or any medication for a length of time, a titration of the amount of drug taken by the patient is necessary in order to achieve the optimal benefit of the drug, and at the same time to prevent any undesirable side effects that taking too much of the drug could produce. Thus, there is a continuous balance between taking enough drug in order to gain the benefits from that drug and at the same time not taking so much drug as to illicit a toxic event.

There is large inter-individual variability in the patient pharmocodynamic and pharmacokinetic interactions of drugs. What may be an appropriate drug dose for one individual, may be too much or too little for another. Prior to this invention a physician was required to estimate the correct drug dosage for a patient and then to experiment with that dosage, usually by trial and error, until the correct dosage was achieved. Likewise, the FDA labeling of a drug suggests dosages based on epidemiological studies and again does not account for inter-individual variability.

Non-linear least squares modeling methods involve the use of large amounts of data relating to a general population in order to calculate a best fit. Much like linear regression models, this method cannot take into account the variability between people with the same population characteristics.

Bayesian analysis is another method used to relate drug dose to efficacy. This method employs large-scale population parameters to stratify a population in order to better characterize the individuals. This method does not take into account the changes that can occur within a person over time, and as a result cannot reliably estimate dosages.

Pharmacokinetic compartment modeling has had success with some drugs, but because the models are static and cannot adapt themselves to changes within a population or a patient, they are once again undesirable for dynamically determining drug dosages.

Expert systems have been developed using similar technology to predict drug dosages for immunosuppressant drugs (see, e.g., U.S. Patent Nos. 5,365,948, 5,542,436 and 5,694,950). These algorithms, however, are not generic and only use immunosuppressant blood levels. Each algorithm is specific to an individual immunosuppressant drug. As it stands, these inventions cannot be applied to other drugs and do not have a non-linear feedback loop mechanism.

SUMMARY OF THE INVENTION

According to the present invention, patient dosing occurs through a cyclic series of events, depicted in flow chart form in Figure 1. After an initial examination, an initial dose of a drug, such as an anticoagulant, is prescribed and administered by a physician for a patient. The initial dose is based on the FDA recommended dosage found on the drug label. The anticoagulant dose is further refined upon repeated dosing by the physician based on the patient's response to the

anticoagulant. Too much anticoagulant could cause the patient to experience toxic anticoagulant effects, and the anticoagulant dose would need to be reduced. Too little anticoagulant could cause the patient not to receive the benefit the anticoagulant therapy could offer, and the dosage would need to be increased.

The preferred embodiment of the invention requires that a physician determine the percentage of response by the patient to the anticoagulant based on the surrogate markers for that anticoagulant. A relationship is then employed which uses the input parameters described above to determine the next dose for the patient.

The invention also includes embodiments focused on specific anticoagulants, such as, for example only, Coumadin®, warfarin, substances containing warfarin, etc. For example, the invention includes a method for calculating a revised dose of Coumadin® for a patient using Coumadin®, comprising the steps of: accepting as a first input the patient's current Coumadin® dose; accepting as a second input a maximum dose of Coumadin®; accepting as a third input a percent response of the patient based on one or more surrogate markers for said patient; and determining a revised dose, wherein said revised dose is a function of said current dose minus a ratio of the percent response of the patient and a ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

Another example is a method for determining a dose of warfarin or a substance containing warfarin for a patient, comprising the steps of: administering an initial dose of Warfarin or said substance containing warfarin to the patient; examining the patient to monitor and characterize one or more numerical surrogate markers; determining if a dose change is necessary; and calculating a revised dose as a function of said current dose minus the ratio of the change in numerical

markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

Each specie of the invention has two preferred embodiments; one which uses actual numerical surrogate markers to calculate a dose, and another embodiment that uses percentages as the numerical input for the surrogate markers.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows a flow chart of the process by which revised doses of an anticoagulant are determined, according to the method of the invention described herein.

Figure 2 shows an apparatus for use in calculating revised doses of an anticoagulant according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

A method of this invention for use in treating a patient receiving an anticoagulant to optimize therapy and to prevent an adverse anticoagulant response can be implemented in two different embodiments, two of which will each be described separately. Figure 1 shows a flow chart of the overall process of treating a patient using this expert system. The actual expert system, however, performs only the steps shown in blocks 10 and 12 of the flow chart.

This expert system includes a general purpose computer, shown in Figure 2, comprising an input means, preferably a keyboard 20 and/or a mouse 22, an output means 30, preferably a video display screen, a data storage means 50, preferably a hard disk drive, and a processor. The expert computer program receives input data from a physician regarding the patient's current anticoagulant dose, the maximal dose range for the anticoagulant, and the percent response of the patient based on the surrogate markers used to monitor the anticoagulant. Also

characterized is the patient's response to the last dosing cycle as well as a dose response constant. This allows the expert system to individualize the patient dosing based on the patient's individual response to the anticoagulant. The system calculates a revised dosage based on the data input by the physician. The software portion of the invention includes a user interface portion 100 to receive the input data and to output the revised dosage information, and a data analysis portion 110, which calculates the new dosage information based on the input data.

Numerical Surrogate Markers Embodiment

A physician prescribes an anticoagulant for a patient based on the FDA recommended dose on the label of the anticoagulant. The physician then re-evaluates the patient, usually daily, either in person or remotely depending on the agent being prescribed. During the subsequent evaluations by the physician, the surrogate markers are monitored and sequentially compared to determine if there are any toxicities associated with the anticoagulant. Also the numerical markers will evaluated to see if the desired effect of the anticoagulant is being achieved. Based on this evaluation by the physician, the current anticoagulant dose, the current anticoagulant numerical marker, the desired anticoagulant numerical marker, and the previous anticoagulant numerical marker are then input into the embodiment and the new anticoagulant dose is calculated based on the equation:

$$NAD = CAD - \{[\langle(CANM - DANM)/CANM\rangle/\langle 1+ (CAD/HIGH)\rangle] \times CAD\} + LV$$

where:

$$LV = \{(RESPONSE \times CAD) \times [(1+D) - (1+E)]/ abs\ (1+D)\} / 1.3^{(CAD/HIGH)}$$

$$E = CANM - PANM$$

$$D = DANM - PANM$$

and wherein:

NAD = New Anticoagulant Dose

CAD = Current Anticoagulant Dose

CANM = Current Anticoagulant Numerical Marker

DANM = Desired Anticoagulant Numerical Marker

PANM = Previous Anticoagulant Numerical Marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

Percentage Surrogate Markers Embodiment

In this preferred embodiment, a physician prescribes an anticoagulant for a patient based on the FDA recommended dose on the label of the anticoagulant. The physician then re-evaluates the patient, usually daily, either in person or remotely depending on the agent being prescribed. During the subsequent evaluations by the physician, the surrogate markers are monitored and sequentially compared to determine if there are any toxicities associated with the anticoagulant. Also the surrogate markers are evaluated to see if the desired effect of the anticoagulant is being achieved. Based on this evaluation by the physician, the current anticoagulant dose, and the percent response of the patient to the last dosing based on a surrogate marker are then input into the system and the new anticoagulant dose is calculated based on the equation:

$$NAD = CAD - \{[\langle(PAR - 100)/PAR\rangle/\langle 1+ (CAD/HIGH)\rangle] \times CAD\} + LV$$

where:

$$LV = \{(RESPONSE \times CAD) \times [(100 - RES) \times 0.01]\} / 1.3^{(CAD/HIGH)}$$

and wherein:

NAD = New Anticoagulant Dose

CAD = Current Anticoagulant Dose

PAR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

This cycle of repeated re-evaluation of the numerical surrogate markers is continued as long as the patient is required to take the anticoagulant.

Two embodiments of the invention have been described, one using numerical markers, and one using a percentage surrogate marker.

Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those of ordinary skill in the art without departing from the spirit and scope of the invention as defined by the following claims, including all equivalents thereof.

CLAIMS

1. A method for calculating a revised dose of an anticoagulant for a patient using said anticoagulant, comprising the steps of:

accepting as a first input the patient's current anticoagulant dose;

accepting as a second input a maximum dose of the anticoagulant;

accepting as a third input a percent response of the patient based on one or more surrogate markers for said patient; and

determining a revised dose, wherein said revised dose is a function of said current dose minus a ratio of the percent response of the patient and a ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

2. The method of claim 1, wherein:

said determining step includes determining said revised dose based on the equation

RAD = CAD - {[⟨(PAR - 100)/PAR⟩/⟨1+ (CAD/HIGH)⟩] x CAD} + LV

where:

LV = {(RESPONSE x CAD) x [(100 - RES) x 0.01]} / 1.3^(CAD/HIGH)

and wherein:

RAD = Revised Anticoagulant Dose

CAD = Current Anticoagulant Dose

PAR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

3. The method of claim 1, wherein:

said anticoagulant is selected from a group comprising warfarin, Coumadin®, heparin, warfarin sodium salt, coumarin derivatives, indandione derivatives, dicumarol, anisindione, phenindione, ethyl bicoumacetate, bishydroxycoumarin, abcimixab, Reopro®, actilyse, alteplase, Activase®, anagrelide, Agrylin®, anistreplase, Eminase®, antithrombin III, Thrombate III®, ardeparin, Normiflo®, argatroban, clopidrogel, Plavix®, dalteparin, Fragmin®, danaparoid, Orgaran®, dipyridamole, Persantine®, dipyridamole/aspirin, Aggrenox®, duteplase, enoxaparin, Lovenox®, eptifibatide, Integrilin®, lepirudin, Refludan®, nadroparin, Fraxiparine®, oprelvekin, Neumega®, pentosan polysulfate sodium, Elmiron®, reteplase, Retavase®, reviparin, Clivarine®, saruplase, streptokinase, Kabikinase®, Streptase®, tinzaparin, Innohep®, tirofiban, Aggrastat®, unfractionated heparin, low molecular weight heparin, all antithrombotic agents, all vitamin K antagonists, and all substances derived from and/or related to the foregoing substances.

4. A method for calculating a revised dose of a anticoagulant for a patient using said anticoagulant comprising the steps of:

accepting as a first input the patient's current anticoagulant dose;

accepting as a second input the maximum dose of the anticoagulant;

accepting as a third input one or more numerical markers indicating a response of the patient; and

calculating said revised dose, wherein said revised dose is a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

5. The method of claim 4, wherein:

said calculating step includes calculating said revised dose based on the equation

RAD = CAD - {[⟨(CANM - DANM)/CANM⟩/⟨1+ (CAD/HIGH)⟩] x CAD} + LV

where:

LV = {(RESPONSE x CAD) x [(1+D) - (1+E)]/ abs (1+D)} / 1.3^(CAD/HIGH)

E = CANM - PANM

D = DDNM - PDNM

and wherein:

RAD = Revised Anticoagulant Dose

CAD = Current Anticoagulant Dose

CANM = Current Anticoagulant Numerical Marker

DANM = Desired Anticoagulant Numerical Marker

PANM = Previous Anticoagulant Numerical Marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

6. The method of claim 4, wherein:

said anticoagulant is selected from a group comprising warfarin, Coumadin®, heparin, warfarin sodium salt, coumarin derivatives, indandione derivatives, dicumarol, anisindione, phenindione, ethyl bicoumacetate, bishydroxycoumarin, abcimixab, Reopro®, actilyse, alteplase, Activase®, anagrelide, Agrylin®, anistreplase, Eminase®, antithrombin III, Thrombate III®, ardeparin, Normiflo®, argatroban, clopidrogel, Plavix®, dalteparin, Fragmin®, danaparoid, Orgaran®, dipyridamole, Persantine®, dipyridamole/aspirin, Aggrenox®, duteplase, enoxaparin, Lovenox®, eptifibatide, Integrilin®, lepirudin, Refludan®, nadroparin, Fraxiparine®, oprelvekin, Neumega®, pentosan polysulfate sodium, Elmiron®, reteplase, Retavase®, reviparin, Clivarine®, saruplase, streptokinase, Kabikinase®, Streptase®, tinzaparin, Innohep®, tirofiban, Aggrastat®, unfractionated heparin, low molecular weight heparin, all antithrombotic agents, all vitamin K antagonists, and all substances derived from and/or related to the foregoing substances.

7. A method for determining a dose of a anticoagulant for a patient, comprising the steps of:

administering an initial dose of said anticoagulant to the patient;

evaluating the patient to monitor and characterize one or more numerical surrogate markers;

determining, based on said numerical surrogate markers, if a dose change for said anticoagulant is necessary; and

calculating a revised dose as a function of said current dose minus the ratio of a percent response of the patient and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

8. The method of claim 7, wherein:

said anticoagulant is selected from a group comprising warfarin, Coumadin®, heparin, warfarin sodium salt, coumarin derivatives, indandione derivatives, dicumarol, anisindione, phenindione, ethyl bicoumacetate, bishydroxycoumarin, abcimixab, Reopro®, actilyse, alteplase, Activase®, anagrelide, Agrylin®, anistreplase, Eminase®, antithrombin III, Thrombate III®, ardeparin, Normiflo®, argatroban, clopidrogel, Plavix®, dalteparin, Fragmin®, danaparoid, Orgaran®, dipyridamole, Persantine®, dipyridamole/aspirin, Aggrenox®, duteplase, enoxaparin, Lovenox®, eptifibatide, Integrilin®, lepirudin, Refludan®, nadroparin, Fraxiparine®, oprelvekin, Neumega®, pentosan polysulfate sodium, Elmiron®, reteplase, Retavase®, reviparin, Clivarine®, saruplase, streptokinase, Kabikinase®, Streptase®, tinzaparin, Innohep®, tirofiban, Aggrastat®, unfractionated heparin, low molecular weight heparin, all antithrombotic agents, all vitamin K antagonists, and all substances derived from and/or related to the foregoing substances.

9. A method for determining a dose of an anticoagulant for a patient, comprising the steps of :

administering an initial dose of said anticoagulant to the patient;

examining the patient to monitor and characterize one or more numerical surrogate markers;

determining if a dose change is necessary; and

calculating a revised dose as a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

10. A method for calculating a revised dose of an anticoagulant for a patient, comprising the steps of:

accepting as input the patient's current anticoagulant dose;

accepting as input the maximum dose of the anticoagulant;

accepting as input the percent response of the patient based on surrogate markers; and

calculating a revised dose, wherein said revised dose is a function of said current dose, said maximum dose, and said percent response of the patient based on said surrogate markers.

11. A method for calculating a revised dose of an anticoagulant for a patient, comprising the steps of:

accepting as input a patient's current anticoagulant dose;

accepting as input a maximum dose of the anticoagulant;

accepting as input the previous, current and desired values of one or more numerical markers indicating the response of the patient; and

calculating a revised dose, wherein said revised dose is a function of said current dose, said maximum dose, and said previous, current and desired values of said numerical markers.

12. A storage device having stored thereon an ordered set of instructions which, when executed by a computer, performs a method comprising the steps of:

accepting as input a patient's current anticoagulant dose;

accepting as input a maximum dose of the anticoagulant;

accepting as input a percent response of a patient based on surrogate markers; and

calculating a revised dose, wherein said revised dose is a function of said current dose minus the ratio of a percent response of the patient and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

13. The storage device of claim 12, wherein:

said anticoagulant is selected from a group comprising warfarin, Coumadin®, heparin, warfarin sodium salt, coumarin derivatives, indandione derivatives, dicumarol, anisindione, phenindione, ethyl bicoumacetate, bishydroxycoumarin, abcimixab, Reopro®, actilyse, alteplase, Activase®, anagrelide, Agrylin®, anistreplase, Eminase®, antithrombin III, Thrombate III®, ardeparin, Normiflo®, argatroban, clopidrogel, Plavix®, dalteparin, Fragmin®, danaparoid, Orgaran®, dipyridamole, Persantine®, dipyridamole/aspirin, Aggrenox®, duteplase, enoxaparin, Lovenox®, eptifibatide, Integrilin®, lepirudin, Refludan®, nadroparin, Fraxiparine®, oprelvekin, Neumega®, pentosan polysulfate sodium, Elmiron®, reteplase, Retavase®, reviparin, Clivarine®, saruplase, streptokinase, Kabikinase®, Streptase®, tinzaparin, Innohep®, tirofiban, Aggrastat®, unfractionated heparin, low molecular weight heparin, all antithrombotic agents, all vitamin K antagonists, and all substances derived from and/or related to the foregoing substances.

14. A storage device having stored thereon an ordered set of instructions which, when executed by a computer, performs a method comprising the steps of:

accepting as input the patient's current anticoagulant dose;

accepting as input the maximum dose of the anticoagulant;

accepting as input one or more numerical markers indicating the response of the patient; and

calculating a revised dose, wherein said revised dose is a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

15. An apparatus for calculating a revised dose of an anticoagulant for a patient comprising:

means for accepting as input one or more markers which indicate a patient's response to a dose of said anticoagulant;

means for accepting as input the patient's current anticoagulant dose;

means for accepting as input the maximum dose of the anticoagulant; and

means for calculating a revised dose of the anticoagulant as a function of said markers, said current anticoagulant dose, and said maximum anticoagulant dose.

16. The apparatus of claim 15, wherein:

said markers are actual numerical markers

17. The apparatus of claim 15, wherein:

said markers are surrogate markers representing a percent response of the patient to the anticoagulant.

18. The apparatus of claim 15, wherein:

said revised dose is calculated by the equation:

RAD = CAD - {[⟨(CANM - DANM)/CANM⟩/⟨1+ (CAD/HIGH)⟩] x CAD} + LV

where:

LV = {(RESPONSE x CAD) x [(1+D) - (1+E)]/ abs (1+D)} / 1.3^(CAD/HIGH)

E = CANM - PANM

D = DDNM - PDNM

and wherein:

RAD = Revised Anticoagulant Dose

CAD = Current Anticoagulant Dose

CANM = Current Anticoagulant Numerical Marker

DANM = Desired Anticoagulant Numerical Marker

PANM = Previous Anticoagulant Numerical Marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

19. The apparatus of claim 15, wherein:

said revised dose is calculated by the equation:

RAD = CAD - {[⟨(PAR - 100)/PAR⟩/⟨1+ (CAD/HIGH)⟩] x CAD} + LV

where:

LV = {(RESPONSE x CAD) x [(100 - RES) x 0.01]} / 1.3^(CAD/HIGH)

and wherein:

RAD = Revised Anticoagulant Dose

CAD = Current Anticoagulant Dose

PAR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

20. The apparatus of claim 15, wherein:

said anticoagulant is selected from a group comprising warfarin, Coumadin®, heparin, warfarin sodium salt, coumarin derivatives, indandione derivatives, dicumarol, anisindione, phenindione, ethyl bicoumacetate, bishydroxycoumarin, abcimixab, Reopro®, actilyse, alteplase, Activase®, anagrelide, Agrylin®, anistreplase, Eminase®, antithrombin III, Thrombate III®, ardeparin, Normiflo®, argatroban, clopidrogel, Plavix®, dalteparin, Fragmin®, danaparoid, Orgaran®, dipyridamole, Persantine®, dipyridamole/aspirin, Aggrenox®, duteplase, enoxaparin, Lovenox®, eptifibatide, Integrilin®, lepirudin, Refludan®, nadroparin, Fraxiparine®, oprelvekin, Neumega®, pentosan polysulfate sodium, Elmiron®, reteplase, Retavase®, reviparin, Clivarine®, saruplase, streptokinase, Kabikinase®, Streptase®, tinzaparin, Innohep®, tirofiban, Aggrastat®, unfractionated heparin, low molecular weight heparin, all antithrombotic agents, all vitamin K antagonists, and all substances derived from and/or related to the foregoing substances.

21. A method for calculating a revised dose of Coumadin® for a patient using Coumadin®, comprising the steps of:

accepting as a first input the patient's current Coumadin® dose;

accepting as a second input a maximum dose of Coumadin®;

accepting as a third input a percent response of the patient based on one or more surrogate markers for said patient; and

determining a revised dose, wherein said revised dose is a function of said current dose minus a ratio of the percent response of the patient and a ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

22. The method of claim 21, wherein:

said determining step includes determining said revised dose based on the equation

RCD = CCD - {[⟨(PCR - 100)/PCR⟩/⟨1+ (CCD/HIGH)⟩] x CCD} + LV

where:

LV = {(RESPONSE x CCD) x [(100 - RES) x 0.01]} / 1.3^(CCD/HIGH)

and wherein:

RCD = Revised Coumadin® Dose

CCD = Current Coumadin® Dose

PCR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for Coumadin®

RESPONSE = Percent of total dose available for individualizing patient dose

1.3^(CCD/HIGH) = 1.3 raised to an exponent (CCD/HIGH).

23. A method for calculating a revised dose of Coumadin® for a patient using Coumadin®, comprising the steps of:

accepting as a first input the patient's current Coumadin® dose;

accepting as a second input the maximum dose of Coumadin®;

accepting as a third input one or more numerical markers indicating a response of the patient; and

calculating said revised dose, wherein said revised dose is a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

24. The method of claim 23, wherein:

said calculating step includes calculating said revised dose based on the equation

RCD = CCD - {[⟨(CCNM - DCNM)/CCNM⟩/⟨1+ (CCD/HIGH)⟩] x CCD} + LV

where:

LV = {(RESPONSE x CCD) x [(1+D) - (1+E)]/ abs (1+D)} / 1.3^(CCD/HIGH)

E = CCNM - PCNM

D = DCNM - PCNM

and wherein:

RCD = Revised Coumadin® Dose

CCD = Current Coumadin® Dose

CCNM = Current Coumadin® Numerical Marker

DCNM = Desired Coumadin® Numerical Marker

PCNM = Previous Coumadin® Numerical Marker

HIGH = The input parameter that is the high dose range for Coumadin®

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CCD/HIGH) = 1.3 raised to an exponent of (CCD/HIGH).

25. A method for determining a dose of Coumadin® for a patient, comprising the steps of:

administering an initial dose of Coumadin® to the patient;

evaluating the patient to monitor and characterize one or more numerical surrogate markers;

determining, based on said numerical surrogate markers, if a dose change for Coumadin® is necessary; and

calculating a revised dose as a function of said current dose minus the ratio of a percent response of the patient and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

26. A method for determining a dose of Coumadin® for a patient, comprising the steps of :

administering an initial dose of Coumadin® to the patient;

examining the patient to monitor and characterize one or more numerical surrogate markers;

determining if a dose change is necessary; and

calculating a revised dose as a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

27. A method for calculating a revised dose of Coumadin® for a patient, comprising the steps of:

accepting as input the patient's current Coumadin® dose;

accepting as input the maximum dose of Coumadin®;

accepting as input the percent response of the patient based on surrogate markers; and

calculating a revised dose, wherein said revised dose is a function of said current dose, said maximum dose, and said percent response of the patient based on said surrogate markers.

28. A method for calculating a revised dose of Coumadin® for a patient, comprising the steps of:

accepting as input a patient's current Coumadin® dose;

accepting as input a maximum dose of Coumadin®;

accepting as input the previous, current and desired values of one or more numerical markers indicating the response of the patient; and

calculating a revised dose, wherein said revised dose is a function of said current dose, said maximum dose, and said previous, current and desired values of said numerical markers.

29. A storage device having stored thereon an ordered set of instructions which, when executed by a computer, performs a method comprising the steps of:

accepting as input a patient's current Coumadin® dose;

accepting as input a maximum dose of Coumadin®;

accepting as input a percent response of a patient based on surrogate markers; and

calculating a revised dose, wherein said revised dose is a function of said current dose minus the ratio of a percent response of the patient and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

30. A storage device having stored thereon an ordered set of instructions which, when executed by a computer, performs a method comprising the steps of:

accepting as input the patient's current Coumadin® dose;

accepting as input the maximum dose of Coumadin®;

accepting as input one or more numerical markers indicating the response of the patient; and

calculating a revised dose, wherein said revised dose is a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

31. An apparatus for calculating a revised dose of Coumadin® for a patient comprising:

means for accepting as input one or more markers which indicate a patient's response to a dose of Coumadin®;

means for accepting as input the patient's current Coumadin® dose;

means for accepting as input the maximum dose of Coumadin®; and

means for calculating a revised dose of Coumadin® as a function of said markers, said current Coumadin® dose, and said maximum Coumadin® dose

32. The apparatus of claim 31, wherein:

said markers are actual numerical markers

33. The apparatus of claim 31, wherein:

said markers are surrogate markers representing a percent response of the patient to Coumadin®.

34. The apparatus of claim 31, wherein:

said revised dose is calculated by the equation:

RCD = CCD - {[⟨(CCNM - DCNM)/CCNM⟩/⟨1+ (CCD/HIGH)⟩] x CCD} + LV

where:

LV = {(RESPONSE x CCD) x [(1+D) - (1+E)]/ abs (1+D)} / 1.3^(CCD/HIGH)

E = CCNM - PCNM

D = DCNM - PCNM

and wherein:

RCD = Revised Coumadin® Dose

CCD = Current Coumadin® Dose

CCNM = Current Coumadin® Numerical Marker

DCNM = Desired Coumadin® Numerical Marker

PCNM = Previous Coumadin® Numerical Marker

HIGH = The input parameter that is the high dose range for Coumadin®

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CCD/HIGH) = 1.3 raised to an exponent of (CCD/HIGH).

35. The apparatus of claim 31, wherein:

said revised dose is calculated by the equation:

RCD = CCD - {[⟨(PCR - 100)/PCR⟩/⟨1+ (CCD/HIGH)⟩] x CCD} + LV

where:

LV = {(RESPONSE x CCD) x [(100 - RES) x 0.01]} / 1.3^(CCD/HIGH)

and wherein:

RCD = Revised Coumadin® Dose

CCD = Current Coumadin® Dose

PCR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for Coumadin®

RESPONSE = Percent of total dose available for individualizing patient dose

1.3^(CDD/HIGH) = 1.3 raised to an exponent of (CDD/HIGH).

36. A method for calculating a revised dose of warfarin or a substance containing warfarin for a patient using warfarin or said substance containing warfarin, comprising the steps of:

accepting as a first input the patient's current warfarin or said substance containing warfarin dose;

accepting as a second input a maximum dose of warfarin or said substance containing warfarin;

accepting as a third input a percent response of the patient based on one or more surrogate markers for said patient; and

determining a revised dose, wherein said revised dose is a function of said current dose minus a ratio of the percent response of the patient and a ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

37. The method of claim 36, wherein:

said determining step includes determining said revised dose based on the equation

RWD = CWD - {[〈(PWR - 100)/PWR〉/〈1+ (CWD/HIGH)〉] x CWD} + LV

where:

LV = {(RESPONSE x CWD) x [(100 - RES) x 0.01]} / 1.3^(CWD/HIGH)

and wherein:

RWD = Revised Warfarin or said substance containing warfarin Dose

CWD = Current Warfarin or a substance containing warfarin Dose

PWR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for warfarin or said substance containing warfarin

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CWD/HIGH) = 1.3 raised to an exponent of (CWD/HIGH).

38. A method for calculating a revised dose of warfarin or a substance containing warfarin for a patient using warfarin or said substance containing warfarin comprising the steps of:

accepting as a first input the patient's current warfarin or said substance containing warfarin dose;

accepting as a second input the maximum dose of warfarin or said substance containing warfarin;

accepting as a third input one or more numerical markers indicating a response of the patient; and

calculating said revised dose, wherein said revised dose is a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

39. The method of claim 38, wherein:

said calculating step includes calculating said revised dose based on the equation

RWD = CWD - {[⟨(CWNM - DWNM)/CWNM⟩/⟨1+ (CWD/HIGH)⟩] x CWD} + LV

where:

LV = {(RESPONSE x CWD) x [(1+D) - (1+E)]/ abs (1+D)} / 1.3^(CWD/HIGH)

E = CWNM - PWNM

D = DWNM - PWNM

and wherein:

RWD = Revised Warfarin or said substance containing warfarin Dose

CWD = Current Warfarin or said substance containing warfarin Dose

CWNM = Current Warfarin or said substance containing warfarin Numerical Marker

DWNM = Desired Warfarin or said substance containing warfarin Numerical Marker

PWNM = Previous Warfarin or said substance containing warfarin Numerical Marker

HIGH = The input parameter that is the high dose range for warfarin or said substance containing warfarin

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CWD/HIGH) = 1.3 raised to an exponent of (CWD/HIGH).

40. A method for determining a dose of warfarin or a substance containing warfarin for a patient, comprising the steps of:

administering an initial dose of warfarin or said substance containing warfarin to the patient;

evaluating the patient to monitor and characterize one or more numerical surrogate markers;

determining, based on said numerical surrogate markers, if a dose change for warfarin or said substance containing warfarin is necessary; and

calculating a revised dose as a function of said current dose minus the ratio of a percent response of the patient and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

41. A method for determining a dose of warfarin or a substance containing warfarin for a patient, comprising the steps of :

administering an initial dose of warfarin or said substance containing warfarin to the patient;

examining the patient to monitor and characterize one or more numerical surrogate markers;

determining if a dose change is necessary; and

calculating a revised dose as a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

42. A method for calculating a revised dose of warfarin or a substance containing warfarin for a patient, comprising the steps of:

accepting as input the patient's current warfarin or said substance containing warfarin dose;

accepting as input the maximum dose of warfarin or said substance containing warfarin;

accepting as input the percent response of the patient based on surrogate markers; and

calculating a revised dose, wherein said revised dose is a function of said current dose, said maximum dose, and said percent response of the patient based on said surrogate markers.

43 . A method for calculating a revised dose of warfarin or a substance containing warfarin for a patient, comprising the steps of:

accepting as input a patient's current warfarin or said substance containing warfarin dose;

accepting as input a maximum dose of warfarin or said substance containing warfarin;

accepting as input the previous, current and desired values of one or more numerical markers indicating the response of the patient; and

calculating a revised dose, wherein said revised dose is a function of said current dose, said maximum dose, and said previous, current and desired values of said numerical markers.

44. A storage device having stored thereon an ordered set of instructions which, when executed by a computer, performs a method comprising the steps of:

accepting as input a patient's current warfarin or a substance containing warfarin dose;

accepting as input a maximum dose of warfarin or said substance containing warfarin;

accepting as input a percent response of a patient based on surrogate markers; and

calculating a revised dose, wherein said revised dose is a function of said current dose minus the ratio of a percent response of the patient and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

45. A storage device having stored thereon an ordered set of instructions which, when executed by a computer, performs a method comprising the steps of:

accepting as input the patient's current warfarin or a substance containing warfarin dose;

accepting as input the maximum dose of warfarin or said substance containing warfarin;

accepting as input one or more numerical markers indicating the response of the patient; and

calculating a revised dose, wherein said revised dose is a function of said current dose minus the ratio of the change in numerical markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

46. An apparatus for calculating a revised dose of warfarin or a substance containing warfarin for a patient, comprising:

means for accepting as input one or more markers which indicate a patient's response to a dose of warfarin or said substance containing warfarin;

means for accepting as input the patient's current warfarin or said substance containing warfarin dose;

means for accepting as input the maximum dose of warfarin or said substance containing warfarin; and

means for calculating a revised dose of warfarin or said substance containing warfarin as a function of said markers, said current warfarin or said substance containing warfarin dose, and said maximum warfarin or said substance containing warfarin dose

47. The apparatus of claim 46, wherein:

said markers are actual numerical markers

48. The apparatus of claim 46, wherein:

said markers are surrogate markers representing a percent response of the patient to warfarin or said substance containing warfarin.

49. The apparatus of claim 46, wherein:

said revised dose is calculated by the equation:

RWD = CWD - {[〈(CWNM - DWNM)/CWNM〉/〈1+ (CWD/HIGH)〉] x CWD} + LV

where:

LV = {(RESPONSE x CWD) x [(1+D) - (1+E)]/ abs (1+D)} / 1.3^(CWD/HIGH)

E = CWNM - PWNM

D = DWNM - PWNM

and wherein:

RWD = Revised Warfarin or said substance containing warfarin Dose

CWD = Current Warfarin or said substance containing warfarin Dose

CWNM = Current Warfarin or said substance containing warfarin Numerical Marker

DWNM = Desired Warfarin or said substance containing warfarin Numerical Marker

PWNM = Previous Warfarin or said substance containing warfarin Numerical Marker

HIGH = The input parameter that is the high dose range for warfarin or said substance containing warfarin

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CWD/HIGH) = 1.3 raised to an exponent of (CWD/HIGH).

50. The apparatus of claim 46, wherein:

said revised dose is calculated by the equation:

RWD = CWD - {[⟨(PWR - 100)/PWR⟩/⟨1+ (CWD/HIGH)⟩] x CWD} + LV

where:

LV = {(RESPONSE x CWD) x [(100 - RES) x 0.01]} /1.3^(CWD/HIGH)

and wherein:

RWD = Revised Warfarin or said substance containing warfarin Dose

CWD = Current Warfarin or said substance containing warfarin Dose

PWR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for warfarin or said substance containing warfarin

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CWD/HIGH) = 1.3 raised to an exponent of (CWD/HIGH).

ABSTRACT

A method and system for use in treating a patient receiving an anticoagulant or a substance containing warfarin to optimize therapy and prevent an adverse drug response. This system employs surrogate markers or indicators including blood levels of the anticoagulant to determine the next required dose for a patient. Since the surrogate markers are employed as a percent change in status, virtually any indicator can be used. Surrogate markers could include any measure of the effectiveness of the anticoagulant's action. Given the effectiveness of the anticoagulant's action relative to the surrogate markers, a change in anticoagulant dose is calculated by the system. Conversely, by employing this system, one could determine the expected result of the anticoagulant dose change on the surrogate markers.

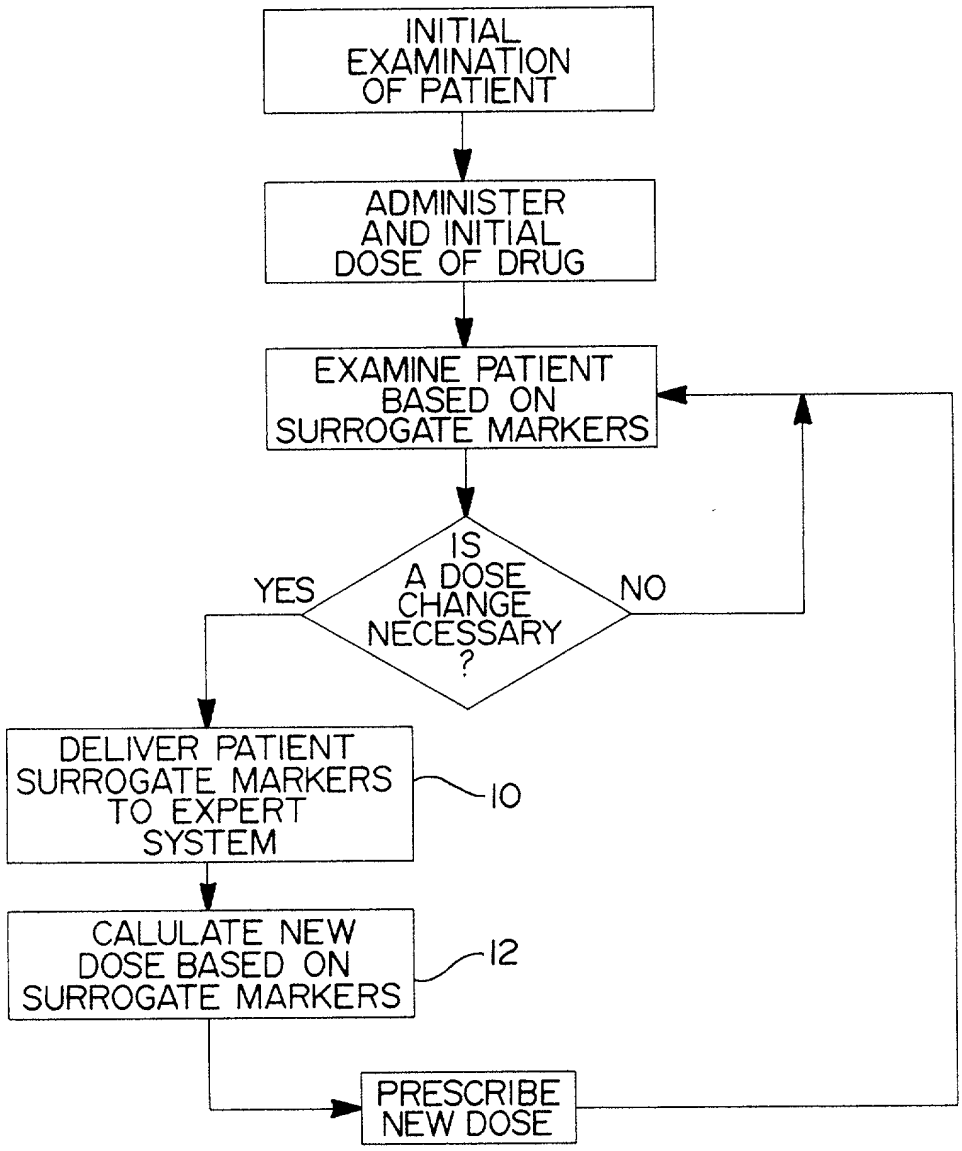
INITIAL EXAMINATION OF PATIENT
ADMINISTER AND INITIAL DOSE OF DRUG
EXAMINE PATIENT BASED ON SURROGATE MARKERS
IS A DOSE CHANGE NECESSARY ?
YES
NO
DELIVER PATIENT SURROGATE MARKERS TO EXPERT SYSTEM
10
CALULATE NEW DOSE BASED ON SURROGATE MARKERS
12
PRESCRIBE NEW DOSE

FIG 1

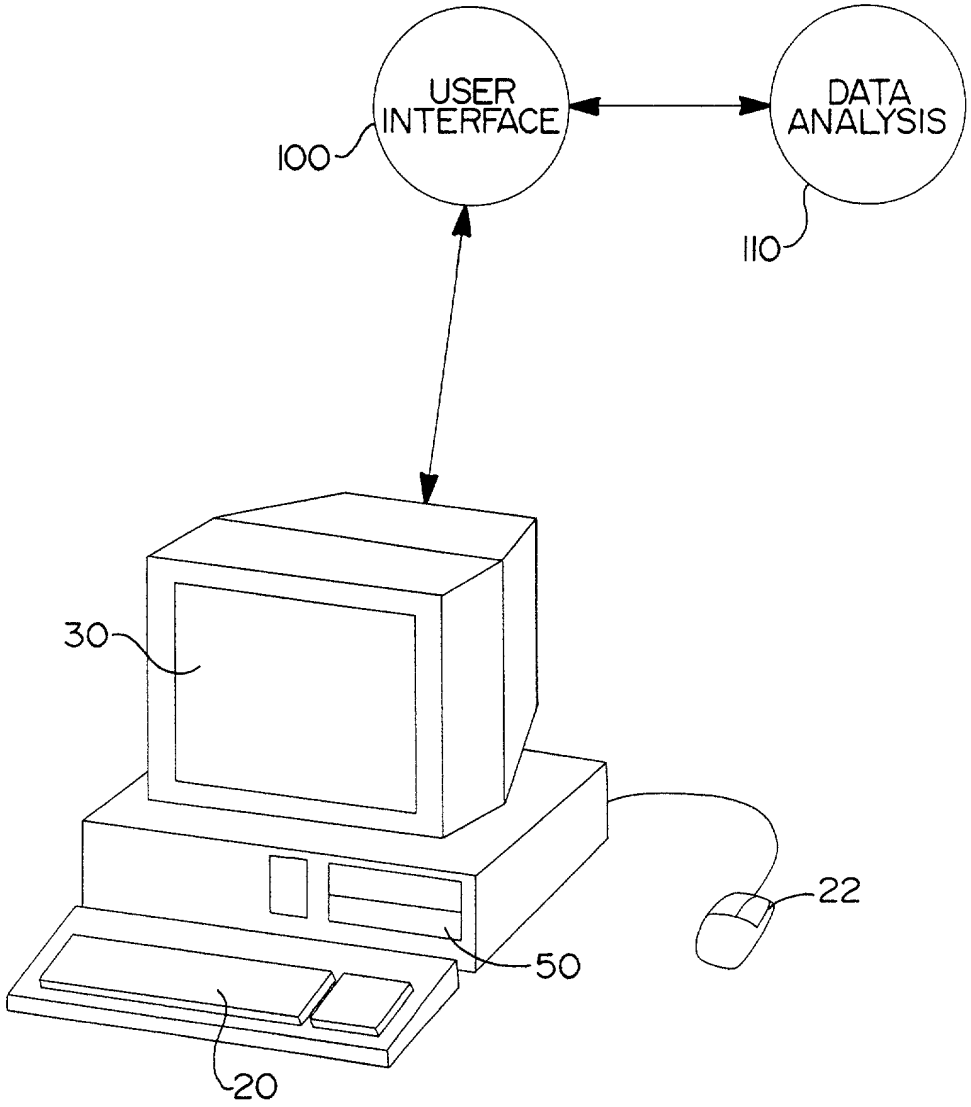

FIG 2

Atty Dkt SMG200A1

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled METHOD AND SYSTEM FOR USE IN TREATING A PATIENT WITH AN ANTICOAGULANT TO OPTIMIZE THERAPY AND PREVENT AN ADVERSE DRUG RESPONSE, the specification of which is attached hereto.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37, Code of Federal Regulations, § 1.56, and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) on which priority is claimed.

Prior Foreign Application(s): NONE.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

NONE

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Serial Number 09/348,592 filed July 6, 1999

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Irving M. Weiner, Reg. No. 22,168, and Pamela S. Burt, Reg. No. 27,861.

SEND CORRESPONDENCE TO: Irving M. Weiner
Weiner & Burt, P.C.
635 N. US-23, P.O. Box 186
Harrisville, MI 48740.

DIRECT TELEPHONE CALLS TO: Irving M. Weiner, (517) 724-7400

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: JOHN D. KUTZKO

Inventor's signature _____ 8/8/00
Date

Country of Citizenship: United States of America
Residence: NOKOMIS, FLORIDA
Post Office Address: 109 LOUELLA LANE
NOKOMIS, FL 34275

Full name of second inventor: MICHAEAL G. SINGER

Inventor's signature _____ 8/8/00
Date

Country of Citizenship: United States of America
Residence: HARRISVILLE, MICHIGAN
Post Office Address: 705 SOUTH LAKE HURON SHORE ROAD
HARRISVILLE, MI 48740

Full name of third inventor: JOHN McMICHAEL

Inventor's signature _____ 8/8/00
Date

Country of Citizenship: Canada
Residence: WEXFORD, PENNSYLVANIA
Post Office Address: 2465 DOGWOOD DRIVE
WEXFORD, PA 15090